Drug Master Files

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INTRODUCTION

In most cases, in order to market a new drug or generic drug in the United States, the manufacturer must file a drug application with the Food and Drug Administration (FDA). The FDA must review and approve the drug application. In support of the application, the manufacturer can reference the information that is filed with the FDA in a Drug Master File (DMF). This information is confidential and the technical contents of a DMF are (usually) only reviewed when authorized by the DMF holder and reviewed only in connection with the review of an Investigational New Drug (IND), New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or an Export Application. A company that intends to conduct a clinical investigation on an approved drug must file an IND. A drug company that wants to market a new drug or a previously approved drug in a new container or a new formula must file a NDA. A company that wants to market a generic drug must file a ANDA. A company that wants to export a drug that is not approved for marketing in the United States must file an Export Application submitted under Section 802 of the Federal Food, Drug, and Cosmetic Act. The DMF is a critical part of the review process and is in increasing use. For this reason, many drug applicants will not use a supplier who does not have a Drug Master File. Drug Master Files are not accepted or rejected, but are rather found to be satisfactory or deficient in support of the drug application in which they are provided. Marketing a pre-1938 drug or a drug for which an Over The Counter (OTC) Monograph status has been granted does not require the filing of an application with the FDA.

FDA—ORGANIZATION

The FDA is divided into different centers, each with their own set of regulations and areas of responsibility.[1] These centers and their areas of responsibility are as follows:

- CSFAN—The Center for Food Safety and Nutrition: Responsible for regulating foods, dietary supplements, and cosmetics.
- CBER—The Center for Biological Evaluation and Research: Responsible for regulating biologics, blood.
- CDRH—The Center for Devices and Radiological Health: Responsible for regulating medial devices, kits, and diagnostic solutions.
- CVM—The Center for Veterinary Medicine: Responsible for regulating animal medicine.
- CDER—The Center for Drug Evaluation and Research: Responsible for regulating drugs.

Drug applications filed with the CDER can be for INDs, NDAs, and ANDAs, also known as generics.[2] The CDER, the CBER, and the CVM share access to the same Drug Master Files.

The CDRH does not use DMFs submitted to the CDER, and submissions to the CDRH are not reviewed or used to support drug applications to the CDER. This aspect of the drug review and approval process is important because there is an overlap of responsibility in the use of some materials and components regulated by more than one center. A syringe that is sold on its own merit, without an associated drug, is regulated by the CDRH, while a syringe containing a drug is reviewed by the CDER. There is an internal FDA intercenter agreement that details the divisions of authority. The CDRH would only comment on a component if requested by the CDER reviewer. Therefore filing information to the CDRH on a syringe does not obviate the need to file a DMF to the CDER. The CDER has defined the information that they expect to review in support of a drug application, and the information should appear in the drug submission or a referenced DMF.

DRUG MASTER FILES

A Drug Master File (DMF) is a submission of information to the FDA by a person or a firm.[3] A DMF is filed with the intent to permit a drug applicant to use (incorporate by reference) the information contained in the DMF in support of a drug application or a supplemental change to an approved application without having to disclose the information to the drug applicant. Drug Master Files were originally used as a way for suppliers to file limited confidential or proprietary information with the FDA in sup-

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port of the drug application, while keeping the information confidential from the end user and the competition. In the United States, confidentially is still an important aspect of the process. In Europe, the relationship between the DMF holder and applicant are somewhat different: It is not uncommon for the DMF holder to provide a copy of the Drug Master File to the drug applicant or customer.

Although firms have the option of filing their own DMF or providing the information to an applicant to file in their drug application, there are many disadvantages to having the drug applicant file the information. The holder of the intellectual property would have to confide the information to the applicant, thereby losing control of it. The term ''control'' does not refer only to confidentiality of the information, but also to document control: The tracking and update of changes. For multiple drug applications, the information is repeatedly reviewed for each drug submission. Different reviewers may have different questions based on their areas of expertise or the end use of the material. Therefore the information may be rereviewed with questions and responses repeatedly filed to each individual drug application. Filing DMF-type information in the NDA or ANDA significantly increases the size of the drug submission, and increases the workload for the FDA reviewer. The information must be well controlled and updated with all drug applicants whenever a change occurs. With a DMF, the information is reviewed once, and if found satisfactory, may not be reviewed for 2 years, unless the end user is changed or the information is amended. A record of the satisfactory review is maintained in the FDA computer database and filed in the Drug Master File. The DMF holder does not receive a copy of the review and is only contacted by the FDA if the DMF is found to be deficient.

DRUG MASTER FILE PROCESS

Two copies of the Drug Master File are mailed to the Drug Master Files Staff, located at 12229 Wilkins Avenue, Rockville, Maryland 20852.[4] The Drug Master File staff will audit the nontechnical information for completeness and adequacy for submission. If the key elements are missing, the staff will contact the proposed holder to try to obtain the necessary documents in order to file the DMF. Once the DMFs are determined to be acceptable for filing, the document room staff assigns a DMF number and a letter is sent to the contact person listed in the DMF.

DRUG MASTER FILE FORMAT

The DMF must meet the format requirements.[5] The DMF is submitted as Original and Duplicate jackets, collated, assembled, paginated, and jacketed, using covers obtained from the government printing office. Multiple volumes are numbered, and the paper must be standard U.S. size paper. It is not unusual to receive paper from England or India that is of different size or weight. Because the pages are placed in binders, the left margin should be no smaller than 3/4 in. and the right margin should be no smaller than 1/2 in. The DMF must be submitted in two copies, one with a blue cover and one with a red cover. The jacket covers are purchased from the government printing office and are specifically provided for the DMFs (Fig. 1).

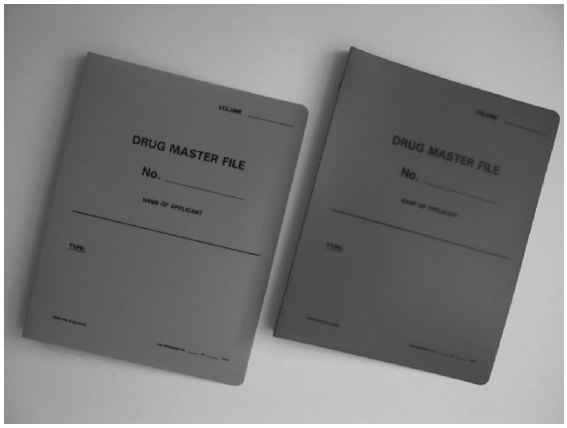

Fig. 1 DMF jackets.

REQUIREMENTS

The regulations for Drug Master Files are listed in the *Code of Federal Regulations* Title 21 § 314.420. In addition, the CDER has issued guidances to better describe the format and provide some suggestions on content. These guidances can be found on the CDER guidances web page www.fda.gov.

A DMF provides (incorporates) information by reference and permits the ''holder'' to ''authorize'' other ''persons'' to disclose information in support of an application. Usually, a DMF may only be accessed (reviewed) by the FDA if the holder of the drug application provides the FDA with authorization (by incorporation), in writing, with two copies, dated, with the DMF number, name of holder, name of material, specific product, reference number/volume, page number, name of authorized persons, and a statement of commitment that the DMF is current. The letters filed to the DMF must have the original signature, typed name, and title of the authorizing person on the letterhead. A copy of each letter is provided to the drug applicant to file in their submission.

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The applicant is not required to acquire a new letter for each submission. The DMF holder usually does not know for which drug an applicant has filed their DMF letter. Regulations governing DMFs are very general. For all DMFs, the following must be provided: The names and addresses of the DMF holder, the corporate headquarters, the manufacturing/processing facility, as well as the name, address, phone number, and fax number for the company contact for FDA correspondence, and the contact information for agent(s), if any. The specific responsibilities of each person listed in any of the above categories should be listed. Including an organization chart with job titles helps to communicate this information. A statement of commitment is required, as well as a signed statement by the holder certifying that the DMF is current, and that the DMF holder will comply with the statements made in the DMF. The commitment letter, a letter appointing the U.S. agent, and any debarment or current Good Manufacturing Practices (cGMPs) statements should all be provided on separate pages.

When a U.S. agent is ''appointed,'' the DMF holder should submit two copies of a letter to the DMF giving the agent's name, address, and scope of responsibility (administrative and/or scientific). Drug Master File holders are not required to appoint an agent, but foreign DMF holders are encouraged to do so. The holder or agent is required to submit archival and duplicate copies and notify each person authorized to incorporate information of changes, additions, or deletions. It should go without saying that the holder must conform to the procedures listed in the DMF.

The DMF should include the name, address, phone number of holder, a description of items that are the subject of the DMF, a list of materials of construction, and the sources of materials of construction. The standards for testing incoming, in process, and release are sometimes different. There are five types of CDER Drug Master Files listed in the *Code of Federal Regulations* Title 21 S314 Drug Master Files (DMF). They are as follows:

- Type 1—Reserved (no longer used; once used for facilities).
- Type 2—Drug substances, intermediates, and materials used in their preparation of drug products.
- Type 3—Packaging materials (resins, compounds, colorants, inks, components).
- Type 4—Excipients (colorants, flavors, and raw materials).
- Type 5: FDA-accepted reference information.

Type 1 Drug Master Files are no longer used. They were once used to describe facilities. In an effort to better define the relationship between the field investigators and the center reviewers, the Center/Field Agreement was written, transferring the responsibility for review of facility information to the field investigator. Facility information on companies that manufacture active ingredients, packaging materials, and raw materials was transferred to the respective Drug Master File.

Type 2 Drug Master Files are required for drug substances, also referred to as active ingredients or active pharmaceutical ingredients. A separate DMF is filed for each active ingredient. The DMF must include a brief description of the facility, the address, a contact, phone number, and fax number. The manufacturing facility must be registered and the number should be listed. A U.S. agent is required to list the active ingredient and register the firm if the site is located outside of the United States. The address should be the same as the address used on the FDA registration form. While a U.S. agent is required for registration, an agent is not required to file a DMF at this time.

Type 2 Drug Master Files should contain a flow diagram of the manufacturing or synthetic process (if it is synthetic) including a list of the critical steps, in-processing tests conducted at those steps, and sampling protocol. The testing of all raw materials should be provided as well as the in-process controls, packaging, release, and stability testing. The impurity profile, particle-size distribution, organic volatile impurities, and residual solvent test results have become increasingly important. These tests should reference the current standards of the United States Pharmacopeia (USP) and the International Conference on Harmonization (ICH) Guidelines. These test results are often compared with those obtained by the end user to validate the results when reviewed by the FDA. If the values are not in agreement, it is a signal that the DMF holder may not be in compliance with the DMF. The testing for polymorphism is increasingly important, and many times is an issue for drug absorption and stability and increasingly in patent litigation. The test methods should be validated if they are not USP. CDER reviewers have standardized the information requirements for Type 2 Drug Master Files through their deficiency letters and guidances.

Guidances for residual solvents, methods validation, changes to the synthetic route, and analytical methods should all be cited in the DMF and used to generate the documentation. As these guidances and test methods evolve, the DMF should be amended to provide for changes and be updated to incorporate changes in USP/NF or FDA standards. The establishment of standards for impurities and residual solvents should not be solely based on the ICH/CDER guidances but should also be established at a low-enough level to demonstrate the control of a process.

Changes in the synthetic route, process, test method, and the loosening of specifications can all have a major impact on the drug application, in which the Drug Master File is referenced. These changes must be classified to

minor or major changes, and a determination must be made as to how these changes are to be reported by the drug company. Changes may require the drug company to manufacture a new test batch with the revised procedure and file a supplement to their approved application before releasing the product to the market. It is in the best interest of the DMF holder to discuss the changes with the end user well in advance of the implementation of the change. Failure to file a change in the DMF, or to notify the end user, can result in regulatory action against the DMF holder. The FDA can also place an embargo on a foreign firm and prevent the import of the active ingredient. The FDA can also ''cancel'' a DMF if the DMF holder does not follow the requirements stated in the Code of Federal Regulations.

The information submitted in Type 3 DMFs is more variable because the articles can be very different. Most Type 3 DMF holders are ISO (International Organization for Standardization) certified, but the rules for ISO and those of CDER are not always the same. There is an increase in the use of Type 3 Drug Master Files for both contract packaging companies and firms that manufacture either components or parts of components. There is a confusion over what is to be filed in packaging DMFs. A Type 3 DMF can contain information on a number of different packaging components. Typically, separate DMFs are filed for closures, plastic bottles, caps, droppers, stoppers, etc. Each packaging material should be identified by the intended use, components, composition, and controls for its release. The names of the suppliers or fabricators of the components used in preparing the packaging material and the acceptance specifications should also be provided. Data supporting the acceptability of the packaging material for its intended use should also be submitted in conformance with the agency's guidances. Toxicological data can be included where appropriate. Components manufactured at alternate sites can still be filed in the same DMF. For example, bottle manufactured at two different plants in the United States can both be in the same DMF. Blister film manufactured in the United States and overseas can be listed in the same DMF. The addresses for both manufacturing facilities would be provided in the facility section of the DMF.

Manufacturers of resins, colorants, inks, compounds, parts, molded components, container systems, and packaging operations all use Type 3 DMFs. Depending on the subject of the DMF, it should contain the following: A short facility description, the formulation providing the trade name, the generic name, *Code of Federal Regulations* Title 21 indirect food additive reference or Food Contact Number, Chemical Abstract number, and references to other supporting DMFs, if applicable. The DMF should list the quality, quantity, and purpose of each chemical in the component compound. A brief description of the manufacturing process, drawings (if applicable), and Certificate of Conformance, with critical-to-function or fit testing should also be included. Test methods should be based on public standards such as ASTM (American Society for Testing and Materials) or USP[3,4] to include physiochemical qualification tests, identity tests, and extractions (USP or other). Firms should specify any additional treatments (such as washing). It is also recommended to include a brief description of packaging and labeling procedures and include samples of labels.

Type 3 DMF holders must be aware of the need to meet additional standards. Certain states and organizations such as the Congress of North East Governors (CONEG), and the states of California and New Jersey have local regulations that must be considered. There are limits for heavy metals, lead, hexavalent chromium, mercury, and cadmium. Mad Cow Certification is required if stearates are used. Testing for Organic Volatile Impurities and residual solvents maybe required. In addition, because most firms ship overseas, international rules may apply as well. Drug Master File holders should follow the FDA regulations and guidances, stay informed, maintain documentation, follow applicable cGMPs, follow DMF practices, and keep customers informed.

The needs of the drug applicant must also be considered. The DMF provide all of the required supporting information on the components that is not contained in the drug submission. Standards and requirements are contained in the USP,[5] FDA, CDER guidances, and ICH/CDER documents. These documents cover most of the testing needed to assure that the components should not adversely impact the drug and render it unacceptable for use. The lower the drug product risk, the more standard the component and its materials, and the easier it is to provide adequate information and meet drug-applicant needs. Standards for high-density polyethylene bottles for a solid oral dosage form are published in the USP <661> and soon to be revised <671> chapters. Solid oral dosage forms are lower-risk products. The standards are understood and have been in place since the 1970s when the standards in the USP chapters were established. Reviewers and manufacturers are well aware of the resins and the properties requirements for this end use.

Where plastic or elastomeric material is used for high-risk products such as inhalation products, injectable drugs, or implants, the risk is greater and the rules are less clear. The FDA provides guidance in this area, but there is a limit as to what help they can provide prior to reviewing the drug product and component information. The drug applicant is placed in a position of trying to test for extractables from the component without knowing what they are, and the DMF holder is trying to

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meet the needs of the customer without compromising their product(s).

The end user does not usually inform the DMF holder as to the product for which the component will be used. It is not unusual for the drug applicant to request a sample supply and a letter of authorization. The DMF holder may be unaware of the status of their DMF. The end user would benefit by telling the DMF holder what the end use of the material or components would be. Through this, the DMF holder can better advise the end user on the choice of components and the degree of testing that they themselves have conducted. The applicant can provide a list of criteria to the DMF holder in advance to be certain the article they purchase meets the product needs. An alternative is to use a confidential third party, to work with both the DMF holder and the drug applicant. With a confidentially agreement signed by both parties, there can be consistency in the information in the DMF. A flow of information from the DMF to the container section of the drug application makes it easier for the FDA to review.

Type 4 Drug Master Files are seldom filed and are not required for raw materials. Most raw materials meet USP/NF standards and need only to meet those criteria for acceptance and certain physical tests. Type 4 DMFs are usually used for flavors and cosmetic coatings for tablets for which USP/NF standards do not exist. Coatings, whether cosmetic or controlled release, may be proprietary in nature. The DMF process allows for these articles to be reviewed, again, under confidentiality. Coatings are usually multiple ingredients. The raw material qualifications, formulation, manufacturing process, and release testing should be provided and iron oxide constituents should be quantitated. It is advisable to include the calculation for iron content for these materials in the DMF.

All DMFs require continuing support. The DMF holder is required to file annual reports and inform the drug applicant of changes to the DMF. The DMF holder must notify each firm authorized to reference the DMF if the DMF holder adds, deletes, or changes information in the DMF. If the holder changes any process or document listed in the DMF, then the DMF must also be changed.

As changes occur, both parties must have a clear understanding of the impact of the change, the method of reporting the change, and the time for the FDA to review the change, if necessary. Changes should be classified based on the cGMPs and the CDER guidances. If the DMF holder is uncertain about the classification of a change or the way in which the drug application should report the changes, it is strongly recommended that the DMF holder contact a regulatory consultant or the agency to discuss the change before it is made. Sufficient information should be provided to the agency in order for the FDA to render a meaningful decision. On the anniversary date of the filing, the holder is to update the DMF to include changes in the authorization list, manufacturing procedures, designs, suppliers, testing, letters of authorization to other DMFs, and provide a complete updated list of people to whom letters of authorization have been issued. Failure to update these items can result in delays in drug approvals. The FDA agencies can also close the DMF based on failure to provide an annual list of persons authorized to incorporate information, failure to provide a list of changes, and failure to provide a statement that the DMF is current.

Based on its experience or newly provided information, the FDA is constantly updating its practices and issuing revised policies and guidances. It is important for both DMF holders and drug applicants to stay vigilant. Documentation and practices should be reviewed on a routine basis and updated to incorporate changes in the regulations, practices, and guidances.

CONCLUSION

The Drug Master File is a critical document used to support a drug application. Deficiencies in the Drug Master File can result in the delay of approval of drug applications. It is important that the DMF be filed in a timely manner and that the standards used to compete it are of the same quality as the actual drug application. The DMF can be considered an extension of the drug application. The drug review process works best when the required information flows from the DMFs to the drug application.

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